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Diagnostic stability in bipolar disorder: a systematic review

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Introduction. Stability of a diagnosis over time represents the best evidence to validate psychiatric diagnoses and helps to predict the course of a disorder. The diagnosis of bipolar disorder shows large variability over time and only a few numbers of investigations have evaluated the impact of the diagnostic stability vs the change.

Material and Methods. A systematic review was made through a literature search in Pubmed, Medline and Web of Science of the articles published in the last 10 years (2008-2018). We used the following key words; "stability diagnosis", AND "bipolar disorders", AND "mood disorders". We selected those studies conducted in patients who presented affective and/or psychotic clinic where the stability of the diagnosis was studied over time.

Results. The initial search showed a total of 140 articles, 13 of which met inclusion criteria. In this review we have found that, compared to other mental disorders, Bipolar Disorder has in its favor a greater construct validity and long-term stability.

Conclusions. Initial phases of Bipolar Disorder constitute a real diagnostic and therapeutic challenge. Despite this, it is considered, added to schizophrenia as one of the most stable diagnostic categories (60% of patients who receive this initial diagnosis remain it during time). The absence of reliable and valid instruments for diagnosis is considered as a limitation so it would be convenient that in the next classifications of mental disorders they continue striving so that the nosological entities have greater construct validity possible.

Keywords: Diagnostic stability, Bipolar disorder, Mood disorders

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Estabilidad diagnóstica en el trastorno bipolar: una revisión sistemática

Introducción. La estabilidad de un diagnóstico psiquiátrico en el tiempo representa la mejor prueba para validarlo y es útil para predecir el curso de un trastorno. El diagnóstico de Trastorno Bipolar presenta gran variabilidad a lo largo del tiempo y son pocas las investigaciones que han evaluado el impacto de la estabilidad diagnóstica *vs* su cambio.

Material y Métodos. Se realizó una revisión sistemática mediante búsqueda bibliográfica en Pubmed, Medline y Web of Science de artículos publicados en los últimos diez años (2008-2018), utilizando las siguientes palabras clave: stability diagnosis, bipolar disorders y mood disorders. Se seleccionaron aquellos estudios realizados en pacientes que presentaban un cuadro afectivo y/o psicótico y en los que se estudiaba la estabilidad temporal del diagnóstico.

Resultados. La búsqueda inicial mostró un total de 140 artículos, de los cuales 13 cumplieron los criterios de inclusión. Hemos encontrado que, en comparación con otros trastornos mentales, en el Trastorno Bipolar se observa una mayor validez de constructo y estabilidad a largo plazo.

Conclusiones. El Trastorno Bipolar en su fase inicial constituye un desafío diagnóstico y terapéutico. Pese a ello, se considera junto con la esquizofrenia una de las categorías diagnósticas más estables (el 60% de los pacientes que reciben este diagnóstico inicial se mantiene en el tiempo). La ausencia de instrumentos fiables y válidos para el diagnóstico es considerada una limitación, por lo que sería conveniente que en sucesivas clasificaciones de los trastornos mentales sigan esforzándose en que las entidades nosológicas tengan la mayor validez de constructo posible.

Palabras clave: Estabilidad diagnóstica, Trastorno bipolar, Trastornos afectivos

INTRODUCTION

Bipolar Disorder (BD) is a serious and recurring mental illness. As such, once the diagnosis is established, it should be stable over time[1].

Diagnostic difficulties complicate the epidemiological study of this disorder, but in general it is accepted a prevalence between 1-2%, regardless of ethnic group[2,3]. According to the WHO, it represents the fifth cause of disability between 15 and 44 years old, and the diagnosis and early intervention proves to be very important to improve the prognosis of this disorder[4].

Although the pathophysiology of BD is not known precisely, studies indicate that there is a large genetic component[5,6]; at least two facts show this: a) there is a concordance in monozygotic twins between 40-70 % in this etiology, and b) the risk of developing the disease in first-degree relatives is 5-10%, that is, seven times higher than in the general population[7]. Even so, the pleomorphic clinical presentation implies the need for a careful diagnostic evaluation to discern BD from other conditions that may present similar characteristics.

According to the international classifications of diseases and mental disorders (the most commonly used ICD-10 and DSM-5), the diagnosis of mental disorders is based on exclusively clinical criteria; no genetic, biochemical, neuroanatomic or neurophysiological findings provide relevant information in the diagnostic processes. This situation has given rise to an important debate about the conceptual validity of the current diagnostic criteria, not exempt from controversy and interpretation[8,9].

Much of the scientific literature is based on the criteria of the American Psychiatric Association (APA), which are purely clinical. Despite this, mania is today one of the most specific concepts of psychiatric nosology[10]. According to the DSM-5 criteria, BD constitutes a spectrum of mood disorders that includes: BD type I, BD type II, cyclothymic disorder, BD and related disorders induced by substance or drugs, BD and related disorders due to another medical condition, other BD and related disorder specified, and BD and related disorder unspecified[11].

This categorical diagnosis is a common resource used for nosological delimitation, therapeutic orientation and the prognosis establishment of people treated in mental health devices. In a pioneering article published in 1970, Robins and Guze[12] mention diagnostic stability as one of the necessary criteria to verify the presence of a psychiatric syndrome and relate it for the first time to the predictive validity of diagnoses in psychiatry[12]. In this context, the temporal diagnostic stability, that is, the degree to which a diagnostic category remains unchanged in the same subjects during successive evaluations over time[13], represents an outstanding criterion of clinical validity of the diagnostic categories[12].

Although a diagnosis established at the beginning may change over time due to different factors (including methodological aspects of diagnostic approach), we can state that, in studies with adequate methodological consistency, the more stable a diagnostic category is the more capacity we have to consider it valid from the psychopathological point of view and assume a certain degree of neurobiological validity[14]. In this way, diagnostic instability questions the categorical model validity with respect to etiology, treatment and prognosis[14].

Diagnostic stability has been defined as the extent to which a diagnosis is confirmed in consecutive evaluations[13]. In the absence of objective biological symptomatology of the disorder, diagnostic stability over time represents the best test to validate psychiatric diagnoses and can largely be used to predict the course of the disorder.

Different methods have been proposed to enhance the stability of a diagnosis, although none of them ensures the reliability of the result. These methods would include the evaluation or longitudinal observation[15,16], advanced genetic diagnostic studies[17], the monitoring of the response to treatment[18] or the evaluation of the effects on psychosocial function of the disease[19].

Diverse studies report a prospective diagnostic consistency (percentage of cases that maintain the same diagnosis in successive evaluations) in a range of 49.7%-96.5% for BD[20-23] and a delay in the diagnosis of up to ten years, generally with a previous diagnosis of the main depressive disorders[24]. In a recent meta-analysis, Ratheesh et al[25], concluded that at least a quarter of patients diagnosed with a Major Depressive Disorder (MDD) will subsequently be diagnosed with BD.

The prevalence of diagnostic errors in the initial evaluation, mostly due to confusion with unipolar depressive episodes, can be between 48% and 69% according to data from research conducted by the National Depressive and Manic-Depressive Association[24,26]. According to López et al.[27], there is a wide range of categories that could act as confounding factors in the diagnosis of BD, which confers great variability over time in the diagnosis of these patients.

In many cases diagnostic changes occur during the course of the disorder, especially towards diagnoses of the schizophrenia spectrum[1,28].

Genetic, neuroanatomy and neurophysiology recent studies of psychotic disorders and bipolar affective disorders show significant overlaps between both groups[9,29-31], and it is not possible to establish a clear neurobiological delimitation between them. Through follow-up studies, it has been observed that an acute psychotic episode may be the beginning of a subsequent diagnosis of chronic evolution of psychotic or affective disorder[32].

Studies on diagnostic stability using DSM or ICD criteria have not found significant differences between the use of ICD or DSM in terms of diagnostic consistency[33].

Therefore, with the relevant data collected in this introduction and the absence of an analysis on the current state of the subject, we raised the objective of conducting a systematic review of the studies on diagnostic stability in BD.

MATERIAL AND METHODS

We conducted a systematic review of the articles published during the last ten years (2008-2018) through a bibliographic search in Pubmed, Medline, Web of Science and Scielo. We use the following keywords: stability diagnosis, bipolar disorders and mood disorders.

Inclusion criteria:

- Publication date: from January 2008 to the present
- Sample: over eighteen, adding studies that included the adolescent and adult population together
- Study desing: we included previous reviews, original papers, clinical trials, prospective studies and case series.
- Main topic of the study: diagnostic stability of BD
- Publication language: Spanish or English

The computer search was complemented by a manual search of articles related to this topic, including those studying diagnostic stability after a First Psychotic Episode (FPE) or affective. After a more detailed assessment, a total of 13 articles were selected.

Those studies that focused on children and adolescents or had another subject for further study were discarded.

RESULTS

During the article searching process for this review, we have observed that the number of studies focused on the diagnostic stability of psychiatric disorders in the adult population is limited, although it has increased greatly in recent years, focusing on the study of the evolution and diagnostic stability after a FPE. There are few studies on diagnostic stability that focus on BD yet, and the investigations that have evaluated the impact of the diagnostic stability of BD on its continuity and persistence over time or the relationships between the different diagnoses in its evolution are even more scarce[34].

In an initial search we found a total of 140 studies, 52 with prospective or retrospective designs. After a more detailed evaluation and applying the inclusion and exclusion criteria, a total of 13 studies were included in this review (Figure 1).

Table 1 shows a summary of the results obtained after the analysis of the selected articles.

Among the studies analyzed, it is worth highlighting those carried out by Pola Salvatore in 2009[23] and 2011[35], both starting with an initial sample of 517 patients with an initial diagnosis of the FPE.

- In the first study (2009)[23], they collected the prospective 24-month follow-up of the original cohort of 517 patients with an initial diagnosis of FPE. After a more precise diagnostic filiation, diagnostic stability is observed throughout the two years of follow-up in 74% of patients. The diagnoses in which greater stability was observed were BD (96.5% of those who received it initially maintained the diagnosis) and schizophrenia (maintained by 75% of those who initially received it). 17 patients were lost throughout the study.
- In the second study (2011)[35], they again carried out a prospective follow-up for 24 months, based on the cohort (500 patients) resulting from the previous study. The diagnostic stability was also assessed after the initial FPE, in this case it was established in the conclusions not through the rates of diagnostic maintenance, but through the rates of changing it. It was observed that there were more diagnostic changes in the case of schizoaffective disorders (37.5%), BD (25%) and schizophrenia (16.7%).

In line with the study conducted by Salvatore in 2009, we found three other studies:

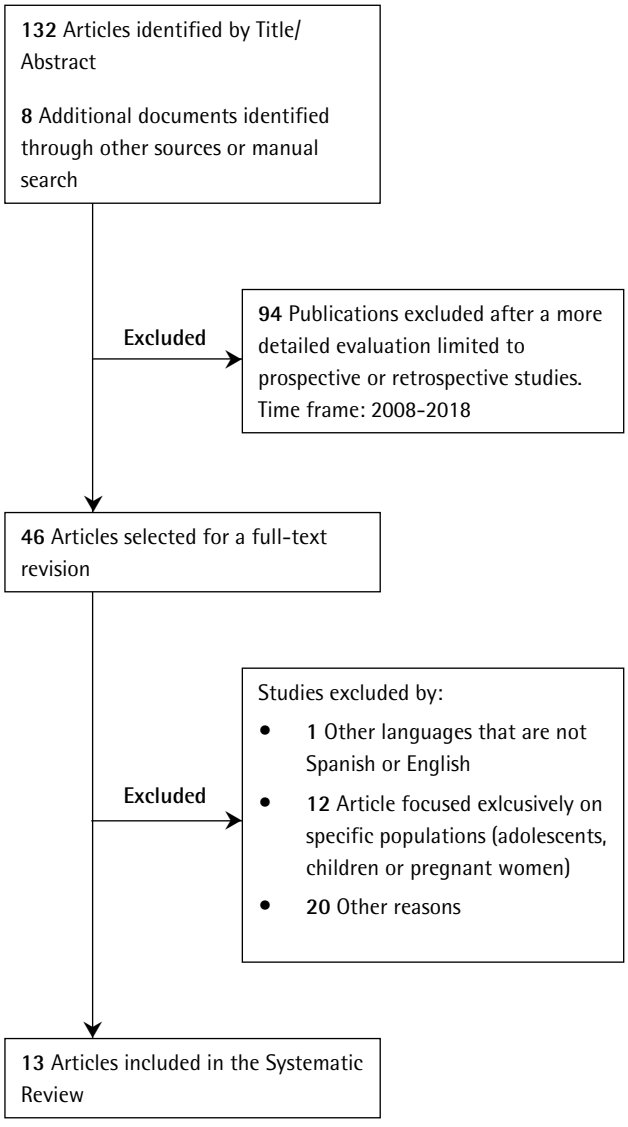

Figure 1 | *Article selection process*

- Kim, 2011[36]: a retrospective study in a cohort of 150 patients with FPE or second psychotic episode. The author made an initial classification in affective and non-affective psychoses through a retrospective review of the medical records, respect to the initial and recurrent diagnosis and clinical characteristics of the first episode. They noted that the diagnostic stability was lower in affective psychoses than in non-affective psychoses (66% *vs* 95.7%). In particular, the diagnostic stability in schizophrenia had greater prospective (91.3%) and retrospective (90.3%) consistency compared to BD, which showed a comparable prospective consistency (86.4%) but a lower retrospective consistency (64.7%).

- Pope, 2013[37]: a study constructed over a 10 year period of follow-ups in a cohort of 214 adults with an initial diagnosis of FPE. It was observed that 76.2% of the diagnoses were maintained after an initial affiliation. The most stable were schizophrenia (92.1% of those who had received it) and BD with psychotic symptoms (84.2% of those who had received it).

- In 2015, Heslin[38] published the results of a study with 10 years of follow-up in a cohort of 403 patients with an initial diagnosis of FPE. In this case, 76% of the sample that received the diagnosis of BD after an initial diagnostic filiation, kept it until the end.

Ruggero[22] published a study in 2010, carrying out a prospective ten-year follow-up of a cohort of 195 patients with an initial diagnosis of psychosis who had received the diagnosis of BD at least in one assessment. 50.3% of the patients maintained the diagnosis of BD from the first visit, observing throughout the follow-up change to a different diagnosis in the rest of the sample.

Studying, rather than diagnostic stability of BD stability other diagnoses that ultimately lead to BD, we also found several articles, including the one published by Dudeck in 2013[39]. This is a retrospective analysis of the long-term evolution (between 15 and 18 years) of a sample of 122 patients with an initial diagnosis of MDD. They observed a diagnostic change to BD in up to 32.8% of the sample, with a diagnostic conversion time (or, equivalently, a delay in the diagnosis of BD) of approximately 9 years[37].

Salvatore[34] also published in 2013 the analysis of 107 patients with an initial diagnosis of depressive disorder with psychotic symptoms, which were followed for an average of 4 years. 18.7% of the sample experienced a diagnostic change to BD and 11.2% to schizoaffective disorder. It was observed that the initial presence of characteristics typically associated with BD or non-affective psychosis was predictive of late diagnostic change to BD or schizoaffective disorder, which highlights the importance of small psychopathological details as a source of improvement of diagnostic criteria and secondarily the prognosis of diseases as complex as those cited.

We should make a special mention to the meta-analysis conducted by Ratheesh[25] and published in 2017. This included a total of 56 studies with patients that were initially diagnosed with MDD (in this case, some studies included children and young people). They assessed the change in

Table 1 Summary of the main features of the articles on diagnostic stability in bipolar disorder included in the review

Authors, year of publication	Study	Sample	Initial diagnosis	Diagnostic criteria	Age (mean, range)	Follow up period	Study variable	Results
Salvatore (2009)[23]	Prospective cohort study	517	FEP	SCID, DSM-IV	Mean age (31.7±13.7)	24 months	Diagnostic stability after FEP	74% maintained diagnostic stability. BD and schizophrenia were the most stable within the diagnostic categories (96.5% and 75% respectively)
Pedrós (2009)[32]	Prospective study	48	Acute psychotic episode	*"Entrevista estructurada para valoración de episodios psicóticos agudos"* (EEVEPA) and DSM-IV criteria	Mean age (28)	24 months	Diagnostic evolution	43.8% of patients change diagnosis, while 56.2% maintain the initial diagnosis of acute psychosis. Among those who experience a change in diagnosis, 47.6% are diagnosed with schizophrenic disorder, 19% with schizoaffective disorder and 14% with BD
Ruggero (2010)[22]	Prospective cohort study	195	Psychosis (received diagnosis of BD at least in one of the evaluations)	Structured clinical interview for DSM-III-R SCID, DSM-IV	Over 18	10 years	Long-term consistency of BD diagnosis	50.3% (n=98) maintained the diagnosis of BD from the first visit. 49.7% (n=97) had a diagnostic change to a non-bipolar disorder during follow-up
Salvatore (2011)[35]	Cohort study	500	Psychotic disorder	SCID, DSM-IV	Mean age (31.7±13.7)	24 months	Diagnostic stability after PEP	The main diagnoses that changed at 24 months were schizoaffective disorder (37.5%), BD (25%) and schizophrenia (16.7%)
Kim (2011)[36]	Retrospective study	150	Psychotic disorder	DSM IV criteria	Age range (13-61)	Not specified	Diagnostic stability and predictive factors associated with diagnostic change	Retrospective consistency of affective psychosis (66%) was much lower than that of non-affective psychosis (95.7%). 9.5% of initial affective disorders were later diagnosed with non-affective psychosis (specifically schizophrenia)
Dudek (2013)[39]	Retrospective study	122	Depressive episode Major depression Unipolar depression Recurrent depression Endogenous depression	CIE-9/10 criteria	Over 18 Mean age (39.8±10.9)	17.1±7 years	Diagnostic stability	32.8% of patients with MDD changed to the diagnosis of BD. Diagnostic conversion time: approximately 9 years

Table 1 Continuation

Authors, year of publication	Study	Sample	Initial diagnosis	Diagnostic criteria	Age (mean, range)	Follow up period	Study variable	Results
Salvatore (2013)[34]	Naturalistic, prospective study	107	MDD with psychotic features	SCID, DSM-IV	Mean age (34.6) Range (10-82)	Variable (2 years or more)	Diagnostic stability	70.1% maintain the diagnosis. In 29.9% there was a diagnostic change: 18.7% for BD and 11.2% for schizoaffective disorder
Pope (2013)[37]	Cohort study	214	FEP	SCID, DSM-IV	Mean age (22.6) Range (14-30)	1 year	Diagnostic stability	76.2% retained their initial diagnosis. The most stable diagnosis was schizophrenia (92.1%) followed by BD with psychotic characteristics (84.2%)
Alavi (2014)[40]	Cohort study	485	BD: 219 Schizophrenia: 59 Schizoaffective disorder: 21 MDD: 92 Anxiety disorder: 5 Delusional disorder: 4 Substance related disorder: 40 Personality disorder: 45	DSM-IV-TR criteria	Mean (38.6±12.7)	6 months	Diagnostic stability	Prospective consistency: - BD 71% - Schizophrenia 55.9% - MDD 41.6 % - Schizoaffective disorder 28.5 Retrospective consistency: - BD 69.4% - Schizophrenia 45.8% - MDD 68.6 % - Schizoaffective disorder 16.6%
Heslin (2015)[38]	Cohorts study	403	FEP	CIE-10 and DMS-IV-TR criteria	Mean (27)	10 years of follow-up	Change diagnosis to another psychotic disorder	76% continue with the initial diagnosis of BD, 3.95% change the diagnosis to another psychotic disorder
Ratheesh (2017)[25]	Meta-analysis	Review of 56 studies	MDD	PRISMA	From childhood to 65	Follow-up for an average of 12-18 years	Change diagnosis from MDD to BD	22.5% of adults and adolescents develop a BD

BD: Bipolar Disorder; FPE: First Psychotic Episode; MDD: Mayor Depressive Disorder

diagnosis from MDD to BD, observing that it took place in up to 22.5% of the population under study.

Regarding the comparison of prospective and retrospective stability of BD, Alavi[40] published in 2014 a study with a cohort of 485 adults with different initial diagnoses. BD showed the highest diagnostic stability, both prospective (71%), followed by schizophrenia; and retrospective (69.4%), followed by MDD.

We can observe that, in general, once the diagnosis of BD is established it presents a more diagnostic stability than other pathologies such as MDD with psychotic symptoms, which end up resulting in a diagnosis of BD.

DISCUSSION

The absence of reliable and valid instruments or tests for the diagnosis of mental disorders continues to be a dramatic limitation for the advancement of knowledge about their etiological, prognostic and therapeutic factors. This is why the successive classifications of mental disorders try to make the nosological entities as valid as possible. This validity is based primarily on epidemiological aspects and clinical observations, assuming that the construct will have the expected behavior and/or remain stable over time.

Diagnostic stability is a relevant concern in mental health as evidenced by the abundance of publications dealing with affective disorders, but despite this extensive literature, the substantial methodological differences between studies continue to complicate the direct comparison of results[41].

The reliability of the diagnoses data confirm the limitation of the diagnostic criteria, perhaps in part because the psychiatric diagnosis is a continuous process that in many cases cannot be made from a single interview[42].

In this context, this review shows that the initial presentation of BD often makes it difficult to differentiate the clinical entity from the disorder. A third of unipolar depressive disorders will change their diagnosis with a delay of almost a decade. This could be due to the fact that there is a considerable percentage of BD whose first manic or hypomanic phase goes unnoticed for different reasons[25,39], because the symptomatology is not usually identified as pathological by the patient and the hypomanic episodes are usually self-limited in time (with a duration of less than seven days according to DSM-5).

Studies that have analyzed diagnostic stability after FPE show that almost 80% are initially detected as BD or schizoaffective. The main diagnostic difficulty from the clinical point of view appears when FPE[22,23,34-36] are accompanied by affective symptoms: if both types of symptoms appear at the same time the diagnosis would be directed to a schizoaffective disorder; on the other hand, when the psychotic symptomatology is secondary to affective symptoms (and more frequently such psychotic symptoms are congruent with mood) the diagnosis would focus on a BD. Therefore, to improve the diagnosis, it is a priority for the clinician to make an effort to take into account longitudinal and evolutionary aspects of the disease, instead of relying on a transverse diagnosis of the condition. It should be noted that these results are limited by the small sample size, the small number of evaluations and the great variability in the duration of follow-up in most of these studies (from 2 to 10 years)[22,23,34-36].

Some limitations of this review have to be taken into account. First, language restrictions imply that this review potentially ignores studies that show other results. A subset of articles with abstracts translated into English or Spanish were analyzed, however, and the conclusions significantly approximated the data obtained. Secondly, we found three studies included in this review[36,39,40] that, although using widely validated criteria such as DSM or ICD for diagnosis, do not use structured interviews for the inclusion of patients in the study. Finally, and inherent to the studied subject, most of the current research is based on short-term follow-up studies, with different methodologies and criteria that can make direct comparison of results difficult. But the similarity between the data obtained and the clinical observation supports the main objective of obtaining a robust systematic review.

CONCLUSION

The early and consistent diagnosis of BD remains an important challenge. The current review shows that about one third of unipolar depressive disorders and a quarter of patients presenting a FPE will change their diagnosis towards BD.

The most consensual presentation of BD is considered as a diagnostic entity with high reliability and stability over time (96.5%). Although we will probably find some lower diagnostic stability in clinical practice.

In order to improve the diagnostic stability of BD, some considerations could be taken into account. In future revisions of the diagnostic manuals, it would be advisable to incorporate, new specifiers that help to increase the validity of the diagnosis (such as the age of onset, predominant polarity or the presence of psychotic symptoms), as well and include other disorders of the bipolar spectrum and sub-threshold symptoms. On the other hand, taking into account a longitudinal view of the diagnosis instead of just relying on cross-sectional assessments of patients could help to generate greater stability. The use of more unified structured interviews, in accordance with actual clinical practice, and the development or use of complementary tests, such as biomarkers or functional imaging studies, could contribute to an improvement in diagnosis.

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